Krabbe Disease: **GALC Gene Sequencing**

### Test Code: KR  
### Turnaround time: 4 weeks  
### CPT Codes: 81479 x1

#### Condition Description

Krabbe disease is an autosomal recessive neurodegenerative disorder caused by a deficiency of the enzyme galactocerebrosidase. It is part of a group of disorders known as leukodystrophies, which result from the abnormal formation of myelin, the protective covering of nerve cells. When the enzyme galactocerebrosidase is deficient it produces toxic substances in the brain resulting in myelin loss, change to brain cells, and neurological damage.

Krabbe disease is characterized by the onset of progressive neurologic deterioration leading to early death. Symptoms of Krabbe disease usually become apparent before two years of age (85%-90% of individuals) or between six months and the fifth decade for those with slower disease progression (10%-15% of individuals). Early symptoms of Krabbe disease include: irritability, excessive crying, stiffness, arrest of motor and mental development, loss of developmental milestones, feeding difficulties, unexplained fevers, hypersensitivity to stimulus, progressive weight loss, and seizures. As the condition progresses, symptoms may include: back arching, jerking of the arms and legs, severe and rapid deterioration of mental and motor function, loss of vision and hearing, and loss of the ability to move or speak. Neuroimaging studies (MRI and/or CT scans) often reveal progressive, diffuse, and symmetrical cerebral atrophy; however, in the early stage of the disease, the MRI and CT scans can be normal.

Mutations in the **GALC** gene cause a deficiency of the enzyme galactosylceramidase. One mutation, a 30kb deletion, accounts for approximately 45% of the mutations in individuals of European ancestry and 35% of the mutations in individuals of Mexican heritage. This large deletion results in the classic infantile form in the homozygous state or when heterozygous with another mutation associated with severe disease. Diagnostic sequencing analysis of the **GALC** gene coding region along with analysis of the 30kb deletion is available for patients with Krabbe disease and their at-risk relatives on a clinical basis.

For questions about testing for Krabbe disease, call EGL Genetics at 470-378-2200. For further clinical information about lysosomal storage diseases, including management and treatment, call the Emory Lysosomal Storage Disease Center at (404) 778-8565 or (800) 200-1524.


#### References:

#### Genes

**GALC**

#### Indications

- Confirmation of a clinical diagnosis of Krabbe Disease
- Prenatal testing for known familial mutations.
- Assessment of carrier status in high risk family members - known mutation analysis.

#### Methodology

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

#### Detection

**Clinical Sensitivity:** 90%

**Analytical Sensitivity:** ~99%

**Prevalence:** The estimated prevalence of all lysosomal storage disorders is 2-5 per 100,000. The prevalence of Krabbe is not specifically known, but is likely to be rare and may vary by ethnicity.

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

#### Specimen Requirements

Submit only 1 of the following specimen types

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* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside EGL Genetics, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

**Related Tests**

- Known Mutation Analysis (KM) is available to test family members.
- A Deletion/Duplication Assay for GALC is available separately for individuals where mutations are not identified by sequence analysis.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor for specific requirements for prenatal testing before collecting a fetal sample.